

ETHYL PARATHION

Toxic Air Contaminant Listing Recommendation

Medical Toxicology Branch  
Department of Pesticide Regulation  
California Environmental Protection Agency

Date: February 10, 1992

## Contributors and Acknowledgments

Principal Author: Nu-may R. Reed, PhD  
Staff Toxicologist  
Health Assessment Section  
Medical Toxicology Branch

Peer Reviewers: Keith Pfeifer, PhD, DABT  
Senior Toxicologist  
Medical Toxicology Branch

Jay Schreider, PhD  
Primary State Toxicologist  
Medical Toxicology Branch

Robert I. Krieger, Chief\*  
Staff Toxicologist  
Worker Health and Safety Branch

\* Currently at Technical Assessment Systems, Inc., Washington, D.C.

## SUMMARY

Ethyl parathion was an organophosphate insecticide-acaricide. In 1988 (Oudiz and Klein, 1988), the Health Effects Document (HED) for the implementation of AB1807 was completed. This document, together with the 1988 HED, formed the basis for recommending the listing of ethyl parathion as a Toxic Air Contaminant (TAC). The use of ethyl parathion was cancelled in 1992.

This document provided an update on the toxicological database and risk assessment. It also presented alternatives for using endpoints other than the inhibition of cholinesterase (ChE) activities in risk assessment. The inhibition of ChE activities is a prominent and well characterized mechanism of toxicity of organophosphates. It was used as the endpoint of toxicity for the risk assessment in the 1988 HED. However, there has been much discussion concerning the biological significance and adversity of the inhibition of ChE activities, especially plasma and red blood cell ChE activities, in the absence of clinical signs or symptoms. The variability in ChE activities and their measurements further contribute to the uncertainty of their use as toxicological endpoints.

Sensitive endpoints from ethyl parathion exposures other than ChE inhibition were identified from studies that were either evaluated in the 1988 HED or submitted after the completion of the 1988 HED. Toxicity endpoints for acute, subchronic, and chronic toxicities included: lacrimation and nasal discharge, ocular function deficit detected by electroretinogram, tremors, and body weight reduction observed in rats. An update of the toxicological database (i.e., genotoxicity and oncogenicity) was also presented.

Acute Toxicity: Two endpoints were used in the risk assessment. Lacrimation and nasal discharge were noted in pregnant rats on day 1 of receiving an oral dose of 0.25 mg/kg/day ethyl parathion, the lowest dose tested. Based on this Lowest-Observed-Effect-Level (LOEL), the No-observed-Effect-Level (NOEL) was estimated to be 0.025 mg/kg/day. Abnormal electroretinogram (ERG) was noted in rats that received a single oral administration of 0.5 mg/kg ethyl parathion. The NOEL was established at the next lower dose of 0.1 mg/kg.

Subchronic Toxicity: Two endpoints were used in the risk assessment. No cholinergic signs were observed in human volunteers that received increasing daily doses of ethyl parathion from 0.003 to 0.05 mg/kg/day in 3 weeks. The time-weighted dose of 0.02 mg/kg/day was established as the subchronic NOEL. Altered pattern of ERG were observed in rats that received 0.4 mg/kg/day ethyl parathion for 3 months through dietary inclusion. The NOEL was established at the next lower dose of 0.04 mg/kg/day.

Chronic Toxicity: Retinal atrophy, tremors, and reduction in body weight gain occurred to rats that received 1.6 mg/kg/day ethyl parathion for 2 years through dietary inclusion. The NOEL was established at the next lower dose of 0.4 mg/kg/day.

Genotoxicity: The overall database indicated that ethyl parathion has genotoxic potential based on positive results in one Ames test, one unscheduled DNA synthesis assay, and a single trial of CHE/HGPRT mutation assay.

Oncogenicity: The total of three studies in rats and two studies in mice were evaluated. Because of the limitations in some of these studies, the determination of the most appropriate approach to evaluating the oncogenic potential in humans was deferred to avoid further delay of regulatory action at this time.

Risk characterization: The risk of a non-oncogenic effect was characterized by the margin-of-safety (MOS), calculated as the ratio of the NOEL to the exposure. The acute MOSs for an off-site exposure at  $34 \text{ ug/m}^3$  (4-hr) were 10-17 based on lacrimation and nasal discharge observed in rats and 38-68 based on ocular functional deficits detected in rats. The acute MOSs for an ambient air exposure at  $1.4 \text{ ug/m}^3$  (24-hr) were 39-69 based on lacrimation and nasal discharge observed in rats and at least 160 based on ocular function deficits detected in rats. The subchronic MOSs were at least 260 based on the lack of clinical signs observed in humans and 510 based on the ocular function deficits detected in rats. The chronic MOSs were above 5,000 based on ocular effects, tremors, and reduction of body weight gain observed in rats.

The uncertainties in the risk assessments were briefly discussed. In general, an MOS of 100, based on endpoints with defined biological significance identified in laboratory animals, is required for the protection of human health. Applying the extra 10-fold factor as specified in the *Criteria for Identifying Pesticides as Toxic Air Contaminants* (Section 6890, Title 3, California Code of Regulation), an MOS below 1,000 will trigger the listing. Ethyl parathion was recommended for listing as a TAC.

## TABLE OF CONTENTS

<u>Page</u>		
I.	Introduction . . . . .	1
II.	Use . . . . .	1
III.	Exposure Assessment . . . . .	2
IV.	Additional Toxicology Information . . . . .	3
	A. Endpoints other than ChE Inhibition . . . . .	3
	B. Update of Toxicological Data . . . . .	6
V.	Risk Characterization . . . . .	11
VI.	Discussion . . . . .	13
VII.	TAC Listing Recommendation . . . . .	13
VIII.	References . . . . .	16
IX.	Appendices	
	Appendix A	
	Appendix B	

## LIST OF TABLES

<u>Page</u>		
Table 1.	Ethyl parathion use report . . . . .	1
Table 2.	The NOELs and LOELs of ethyl parathion for ChE inhibition and other endpoints . . . . .	4
Table 3.	Tumor incidences in rats fed diets containing ethyl parathion. . . . .	9
Table 4.	Tumor incidences in B6C3F1 mice fed diets containing ethyl parathion. . . . .	10
Table 5.	The MOSs for potential exposures to ethyl parathion in air . . . . .	12
Table 6.	Air concentrations corresponding to adequate MOSs for non-oncogenic effects . . . . .	14

## ETHYL PARATHION

### I. INTRODUCTION

Ethyl parathion is an organophosphate insecticide-acaricide registered for use by the U.S. EPA and in California. The Health Effects document (HED) pertaining to AB1807 had been reviewed and approved by the Scientific Review Panel (established pursuant to Section 39670 of the Health and Safety Code). The HED was subsequently published (Oudiz and Klein, 1988).

This document provides the basis for recommending the listing of ethyl parathion as a Toxic Air Contaminant (TAC) according to Section 6890 of Title 3 of the California Code of Regulation, Criteria for Identifying Pesticides as Toxic Air Contaminants. Toxicological data on which the No-Observed-Effect-Levels (NOELs) for risk characterization were based are highlighted, with reference (HED Table number and/or page number) to the HED. Effects other than cholinesterase (ChE) inhibition, when available, are included for a better understanding of the health hazard associated with the margin of safety (MOS) presented in the HED. Updates on use information and toxicological data are also presented.

### II. USE

The total poundage of ethyl parathion active ingredient (ai) used in California during 1983 to 1985 was presented in the HED (HED Table 2, p.8). The update of this information is presented in Table 1.

Table 1. Ethyl parathion use report.

Year	Total use (x 10 <sup>3</sup> lbs)	Total acreage (x 10 <sup>3</sup> acres)	Ave. rate (lbs ai/acre)
1985	756	638	1.19
1986	805	875	0.92
1987	711	597	1.19
1988	765	571	1.34

Because of the concern for risks to workers and wildlife, the U.S. EPA, in September 1991, had reached an agreement with the registrants to limit the use of ethyl parathion to nine field crops (alfalfa, barley, canola, corn, cotton, sorghum, soybeans, sunflowers, and wheat) (U.S.EPA, 1991). The agreement also

included severe restrictions on the application practices. In the initial agreement, the use of the existing stocks, except on eight of the nine approved field crops (the use of canola is pending on data submission), was prohibited after December 31, 1991. This was amended subsequently to allow for the use of certain formulations until July 31, 1992. The impact of the use restriction on the exposure component of the risk assessment is not immediately known.

### III. EXPOSURE ASSESSMENT

The concentrations of ethyl parathion or an ethyl parathion equivalent (when data on ethyl paraoxon were available) used in the HED for characterizing the risk (HED Table 18, p.123; See Appendix A) were:

#### ACUTE EXPOSURE

Source of Data: Maddy et al. 1983; L.A. County;  
2.5 lbs ai/acre (formulation: Phoskil 25); 40 yards  
from application site (HED Table 5C, p.21)  
Max. during application: 33.9 ug/m<sup>3</sup> Parathion  
During 2-hr after 1.5-hr application:  
3.09 ug/m<sup>3</sup> Parathion

Source of Data: ARB's monitoring. Jan. 1986; Northern  
San Joaquin Valley (Fresno Co., Parlier-1 site);  
Concurrent Fresno Co. use report given (HED Fig.2,  
p.53); ambient air (HED Table 6, p.41)  
Max. 24-hr value: 1.423 ug/m<sup>3</sup> (Parathion+Paraoxon)

#### SUBCHRONIC EXPOSURE:

Source of Data: ARB's monitoring. Jan. 1986; Northern  
San Joaquin Valley (Fresno and Tulare Co.; 5 sites);  
Concurrent Fresno Co. use report given (HED Fig.2,  
p.53); ambient air (HED Table 6, p.41)  
Mean 24-hr value: 0.17 ug/m<sup>3</sup> (Parathion+Paraoxon)

#### CHRONIC EXPOSURE:

Subchronic exposure data were also used for chronic exposure.

Woodrow et al (1977) also documented off-site ethyl parathion air concentrations (HED Table 5C, p.21). Unfortunately, a quantitative comparison of these levels to those reported by Maddy et al (1983) was not possible due to different application rates, the distance from the application site, and other technical variations. According to Woodrow et al (1977), the respective parathion and paraoxon concentrations were 1.6 and 0.4 ug/m<sup>3</sup> within 1 hour of 2 lb ai/acre application at 109 yards distance. The 34 ug/m<sup>3</sup> reported by Maddy et al (1983), however, was measured during the

second of a repeated daily application (2.5 lb ai/acre) at 40 yards away. The level at this site decreased to 3.1 ug/m<sup>3</sup> during 2 hours after an approximately 1.5-hour application (HED Table 5C, p.21). No measurement of paraoxon was reported by Maddy et al (1983). In the HED, off-site air concentrations of 3.1 and 34 ug/m<sup>3</sup> were assumed to continue for 4 hours (Appendix A).

#### IV. ADDITIONAL TOXICOLOGY INFORMATION

Information provided in this section addresses endpoints of toxicity other than ChE inhibition for studies from which the NOEL for risk characterization was derived. A few studies have been received after the completion of the HED. An update of the toxicological database is, therefore, also presented in this section. The Summary of Toxicology Data is included in Appendix B.

##### A. ENDPOINTS OTHER THAN ChE INHIBITION

ChE inhibition is frequently identified as the most sensitive endpoint for an organophosphate. The toxicological significance of ChE inhibition in experimental animals, in the absence of cholinergic signs of toxicity, is not clear. Unfortunately, a discussion on clinical observations in the studies from which the NOELs for risk characterization were derived was generally limited. A comparative list of NOEL or lowest-observed-effect-level (LOEL) based on ChE inhibition and other effects is presented in Table 2.

##### 1. ACUTE TOXICITY

An acute inhalation NOEL was established in a study with rats (Owens, 1977). Groups of 34 males were exposed to 20 aerosol concentrations of ethyl parathion (0.035 - 230 mg/m<sup>3</sup>) for 4 hours. ChE was measured in 6 rats at prescribed time intervals. As presented in the HED (HED Table 12, p.89), the 4-hour NOEL was determined at 1.21 mg/m<sup>3</sup>, based on greater than 30% inhibition of plasma and red blood cell (RBC) ChE. Sneezing, nose irritation, diarrhea, urine stain in the scrotal area, lethargy, and "wet dog shakes" were reported at 28.08 mg/m<sup>3</sup>. Death was reported at 50 mg/m<sup>3</sup>. A NOEL associated with endpoints other than ChE inhibition cannot be delineated as the emphasis of this study was on ChE inhibition. Signs of toxicity have been reported in other studies at doses lower than 1.21 mg/m<sup>3</sup>, especially in the females (See subsequent Sections). Sex specific sensitivity has been generally indicated both in the acute toxicity parameters (e.g., LD<sub>50</sub>) and in the dose selections for the various toxicity studies.

NOELs for short-term exposure based on cholinergic signs of toxicity can be delineated from the teratology studies on file in DPR, Cal-EPA. Studies using rabbits and rats were described in the HED (HED p.99). A maternal NOEL of 1 mg/kg/day was established in the rabbit study (Schroeder, 1983b), based on a reduction of body weight gain and ano-genital fur staining at 4 mg/kg/day.

Table 2. The No-Observed-Effect-Levels (NOELs) and Lowest-Observed-Effect-Levels (LOELs) of ethyl parathion for Cholinesterase (ChE) inhibition and other endpoints.

Sp/Sex	Study	ChE Inhibition	Other Toxicity		Ref.
		NOEL/LOEL	Effects	NOEL/LOEL	
<u>ACUTE EXPOSURE</u>					
Rats (M)	Inhal. Acute	1.2 / 2.2 mg/m <sup>3</sup> (4-hr)	nose irritation, diarrhea, shakes	-- / 28 mg/m <sup>3</sup> (4-hr)	(1)
Rats (F)	Inhal. Acute	--	subdued, tremors, death	-- / 12 mg/m <sup>3</sup> (4-hr)	(2)
Rats (M)	Oral Acute	--	sedation, miosis, ataxia, convulsion, death	-- / 2 mg/kg/day (2.1 mg/m <sup>3</sup> )	(3)
Rats (F)	Oral Acute	0.5 / 1.0 mg/kg/day (0.5/1.0 mg/m <sup>3</sup> )	functional impairment of the eye	0.1 / 0.5 mg/kg/day (0.1 / 0.5 mg/m <sup>3</sup> )	(4)
Rats (F)	Oral Teratology	--	lacrimation, nasal discharge	-- / 0.25 mg/kg/day (0.26 mg/m <sup>3</sup> )	(5)
Rabbits (F)	Oral Teratology	--	body weight, ano-genital stain	1 / 4 mg/kg/day (1.9 / 7.4 mg/m <sup>3</sup> )	(6)
<u>SUBCHRONIC EXPOSURE</u>					
Humans	Oral 3-week	0.05*/ -- mg/kg/day (TWA 0.02 mg/kg/day)	no effects observed	0.05*/ -- mg/kg/day (TWA 0.02 mg/kg/day)	(7)
Rats (M)	Inhal. 6-week	0.01 / 0.1 mg/m <sup>3</sup> (7 hr/day, 5 days/wk)	death	0.1 / 0.74 mg/m <sup>3</sup> (7 hr/day, 5 days/wk)	(1)
Rats (F)	Diet 3-month	0.04 / 0.4 mg/kg/day (0.04/ 0.4 mg/m <sup>3</sup> )	functional impairment of the eye	0.04 / 0.4 mg/kg/day (0.04/ 0.4 mg/m <sup>3</sup> )	(8)
Dogs (M)	Inhal. 6-week	0.01 / 0.2 mg/m <sup>3</sup> (7 hr/day, 5 days/wk)	no effects observed	0.2* / -- mg/m <sup>3</sup> (7 hr/day, 5 days/wk)	(1)
<u>CHRONIC EXPOSURE</u>					
Rats (M/F)	Diet 2-year	0.1 / 0.4 mg/kg/day (0.1 / 0.4 mg/m <sup>3</sup> )	ocular effects, tremors, weight reduction	0.4 / 1.6 mg/kg/day (0.4 / 1.5 mg/m <sup>3</sup> )	(9)
Dogs (M/F)	Diet 1-year	0.01 / 0.03 mg/kg/day (0.03/0.08 mg/m <sup>3</sup> )	no effects observed	0.1*/ -- mg/kg/day (0.3 / -- mg/m <sup>3</sup> )	(10)

\*, Highest Dose Tested; TWA, Time-Weighted Average.

References: (1) Owens, 1977; (2) Greenough and McDonald, 1986; (3) Cuthbert and Carr, 1986;  
(4) Atkinson, 1991a; (5) Schroeder, 1983a; (6) Schroeder, 1983b; (7) Rider *et al.*, 1958;  
(8) Atkinson, 1991b; (9) Eiben, 1987; (10) Ahmed, 1981.

In the rat study (Schroeder, 1983a), a decrease in body weight gain (up to 9%) and mortality (4 of the 24 died prior to day 20 of gestation) were noted at 1.5 mg/kg/day (highest dose tested) by gavage. Other cholinergic signs of toxicity, however, were noted at lower doses. High incidences of lacrimation were noted in all treatment groups (0.25, 1.0, and 1.5 mg/kg/day) at day 1 of treatment and throughout the dosing period. Red and clear nasal discharges were also noted in the treated rats, particularly at 1.5 mg/kg/day. Therefore, the LOEL of 0.25 mg/kg/day was established, based on lacrimation as a cholinergic sign of toxicity. Applying the same assumptions used in the HED for rates of respiration (0.96 m<sup>3</sup>/kg/day for rats) and absorption (100% oral and inhalation exposure), this dose level is equivalent to a total inhalation exposure of 0.26 mg/m<sup>3</sup> in 24 hours, or 1.6 mg/m<sup>3</sup> in 4 hours. When a NOEL cannot be established, it is estimated by the default assumption that the NOEL is 10-fold below the LOEL. The NOEL thus estimated was 0.026 mg/m<sup>3</sup> for 24-hour or 0.16 mg/m<sup>3</sup> for 4-hour. This is approximately 8-fold below the NOEL used in the HED and is the lowest NOEL for all endpoints. It is used in this document for assessing the risk of acute exposures.

## 2. SUBCHRONIC TOXICITY

An oral NOEL was established in a study with human volunteers. Eight subjects were given capsules containing parathion, starting at 0.003 mg/kg/day, subsequently at 0.01 mg/kg/day, 0.025 mg/kg/day, and ending at 0.05 mg/kg/day; allowing for 3 weeks of dosing per dose level (Rider et al., 1958). Based on the lack of ChE inhibition and signs of toxicity, the highest dose of 0.05 mg/kg was considered the oral subchronic NOEL (HED Table 13, p.93). A similar study was conducted by Morgan et al. (1977). Ingestion of 1 to 2 mg ethyl parathion for 5 days did not result in any clinical signs of toxicity or ChE inhibition. A basic concern for these studies was the dosing regimen. The interval between each dose level was either lacking or unspecified. A time-weighted dose of 0.02 mg/kg/day from the study by Rider et al. (1958) may be a better estimate of the subchronic NOEL. This value is used in this document for assessing the risk of subchronic exposures.

Two inhalation NOELs, established from the study by Owens et al. (1977) with rats and dogs (HED p.92; HED Table 13, p.93), were also used in the calculation of an MOS. In the rat study, groups of 80 males were exposed to 0.01, 0.1, or 0.74 mg/m<sup>3</sup> of ethyl parathion for 6 weeks. The NOEL in rats, based on ChE inhibition (>30%; RBC), was 0.01 mg/m<sup>3</sup> (7 hr/day, 5 day/week). Death was observed at 0.74 mg/m<sup>3</sup>.

In the dog study, groups of 6 males were exposed to 0.001, 0.01, or 0.2 mg/m<sup>3</sup> ethyl parathion. The NOEL of 0.01 mg/m<sup>3</sup> (7 hr/day, 5 day/week) was also established based on ChE inhibition (>39%; plasma and RBC). No clinical signs of toxicity were observed at any dose level.

### 3. CHRONIC TOXICITY

Oral NOELs established in rats and dogs were used in characterizing the risk of chronic exposure. In the study with rats (Eiben, 1986), groups of 50 rats per sex were fed diets containing 0, 2, 8, or 32 ppm ethyl parathion for 2 years. The NOEL of 2 ppm in diets was established based on ChE inhibition (HED p.104, 120). Body weight gain reduction and tremors were observed at 32 ppm. The evidence of ocular effects based on electroretinogram (ERG) was equivocal but retinal atrophy was noted at 32 ppm in the final report of this study (Eiben, 1987). A NOEL of 8 ppm (0.4 mg/kg/day) was established, based on ocular effects, reduced body weight gain, and tremors. This value is used in this document for assessing the non-oncogenic risk of chronic exposures.

In the study with dogs (Ahmed, 1981), groups of 8 dogs per sex were fed diet containing 0, 0.01, 0.03, or 0.1 mg/kg/day for 1 year. Based on ChE inhibition (>30% plasma and RBC), a NOEL of 0.01 mg/kg/day in dogs was established (HED p. 120). No other endpoints of toxicity were reported. Therefore, the NOEL for endpoints other than ChE inhibition was at or above 0.1 mg/kg/day.

#### B. UPDATE OF TOXICOLOGICAL DATA

Since the completion of the HED in 1988, a few studies for acute and subchronic toxicity, genotoxicity, and combined chronic/ oncogenicity have been received at DPR, Cal-EPA.

#### 1. ACUTE TOXICITY

The recently submitted acute oral, inhalation, and dermal studies, and eye and dermal irritation studies were reviewed by DPR. Ethyl parathion was a category IV eye and dermal irritant. The respective oral LD<sub>50</sub> for male and female rats were 22 mg/kg and 2 mg/kg. The respective dermal LD<sub>50</sub> values for male and female rats were 71 mg/kg and 76 mg/kg. The inhalation (nose-only exposure) LC<sub>50</sub> for rats was 30 mg/m<sup>3</sup>. These values were within the ranges reported in the HED (HED Table 11, p.87). The seemingly higher sensitivity in females, as reflected in the oral LD<sub>50</sub>, was also apparent in some of the acute studies presented in the HED (HED Table 11, p.87); regardless of routes of exposure and species tested.

Although the purpose of these studies was to determine a median lethal dose, a NOEL/LOEL can be estimated from the inhalation and oral studies. In the inhalation study (Greenough and McDonald, 1986), groups of 5 Sprague-Dawley rats per sex were exposed (nose-only) to ethyl parathion at 0.012, 0.034, or 0.151 mg/l for 4 hours. A LOEL at 0.012 mg/l (12 mg/m<sup>3</sup>, 4-hour) was established, based on death, tremors, subdued behavior, and hypokinesia observed in the females at this dose.

In the oral study (Cuthbert and Carr, 1986), groups of 5 male rats received a single gavage at 20, 30, or 40 mg/kg ethyl parathion, and groups of 5 females received 2, 4, or 8 mg/kg ethyl parathion. Sedation, miosis, piloerection, soiled coat, ataxia, clonic convulsion, hemodacryorrhea, salivation, and death were noted at all dose levels. A LOEL of 2 mg/kg was established, based on these effects. The mortality at this dose (1 of 5 rats) was comparable to that reported at 1.5 mg/kg/day (4 of 24 rats) from the rat teratology study (See Section IV.A.1). The comparable findings enhanced the confidence in assessing the risk of acute exposures based the latter study.

## 2. OCULAR EFFECTS

Studies specifically addressing the functional impairment of the eye that may precede histopathological changes associated with ethyl parathion exposure have recently been received.

In a study with rats, ocular effects of ethyl parathion were monitored up to 25 days after a single administration through gavage (Atkinson, 1991a). Groups of 5 males received 0, 2.0, 5.0, 10.0, or 15.0 mg/kg ethyl parathion, and groups of 5 females received 0, 0.1, 0.5, 1.0, or 2.0 mg/kg ethyl parathion. Reversible abnormal electroretinogram (ERG) was noted at and above 1.0 mg/kg. A delayed abnormal ERG was reported at 0.5 mg/kg. Statistically significant ChE inhibition was noted at and above 1.0 mg/kg. The NOEL at 0.1 mg/kg is established based on functional impairment of the eye. This NOEL is also used in this document for assessing the risk of acute exposures. Applying the same assumptions used in the HED for respiration ( $0.96 \text{ m}^3/\text{kg}/\text{day}$  for rats) and absorption (100% oral and inhalation exposure), this dose level is equivalent to a total inhalation exposure of  $0.1 \text{ mg}/\text{m}^3$  in 24 hours, or  $0.63 \text{ mg}/\text{m}^3$  in 4 hours.

A 3-month rat study and a 6-month dog study were available. In the rat study (Atkinson, 1991b), groups of 10 females received 0, 0.04, 0.4, or 4.0 mg/kg/day ethyl parathion through dietary inclusion. Microscopic and ophthalmological evaluation did not reveal any treatment-related changes. Alterations in ERG, including an increase in latency and an decrease in amplitude of the b-wave, were noted at 0.4 and 4.0 mg/kg/day. Plasma and RBC ChE was also inhibited at these levels. A subchronic NOEL of 0.04 mg/kg/day was established, based on the functional impairment of the eye. This is also used in this document for assessing the risk of subchronic exposures.

In the 6-month dog study (Atkinson, 1991c), groups of 5 beagle dogs per sex were administered ethyl parathion via gelatin capsules at 0, 0.0024, 0.0079, or 0.7937 mg/kg/day. Ophthalmological and histopathological examinations and ERG revealed no treatment-related effects. Plasma ChE were inhibited at the mid- and high doses; RBC and brain ChE were inhibited at the high dose.

### 3. GENOTOXICITY

Ethyl parathion was positive in a single trial of CHO/HGPRT mutation assay (DPR, 1990). No effects were noted in an in vivo micronucleus assay in mice, a dominant lethal test in male mice, and an in vitro unscheduled DNA synthesis assay in rat primary hepatocytes. The database as a whole (see HED, p.110 for previously presented information) indicated that ethyl parathion has genotoxic activity. The genotoxicity tests that yielded positive results included: one Ames test, one unscheduled DNA synthesis assay, and the aforementioned CHO/HGPRT assay.

### 4. ONCOGENICITY

Since the completion of the HED, DPR received the final report for the 2-year rat study (Eiben, 1987) and a mouse oncogenicity study. Together with the previously reviewed studies, the evidence of oncogenicity in rats and mice was evaluated.

#### Studies in rats

A total of 3 studies in rats were available for the evaluation of oncogenicity. In the study by Eiben (1987), a statistically significant trend of increases in pancreatic exocrine adenoma/carcinomas and islet adenomas were noted in the males (Table 3). The occurrence of pancreatic tumors is rare. The historical incidences from a total of 22 studies for the same source of Wistar rats were 8/2,422 (0.3%) for the exocrine adenoma and 16/2,427 (0.7%) for the islet cell adenoma (Eiben, 1989). The incidences for these tumors in the mid- and high dose exceeded these historical values. The positive trend of increase in exocrine hyperplasia added to the biological significance of the tumors observed in this study.

The deficiencies of the NCI study (1979) with Osborne-Mendel rats were discussed in the HED document (HED p.113). Among these were the small control groups (10 per sex), less than lifetime dosing (80 weeks), and the change in dosing levels at week 13. These deficiencies, however, did not invalidate the demonstrated evidence of oncogenicity. The incidences of adrenal cortical adenoma/carcinoma in the mid- and high dose males and the high dose females were statistically significantly higher than both the pooled and matched controls (Table 3). The pancreatic islet cell carcinomas in the males showed a statistically significant trend when the incidence from a pooled control was used. The occurrence of malignant tumors added to the weight of oncogenic evidence demonstrated in the aforementioned study by Eiben (1987) in which only adenomas of islet cells were observed.

The third study with Sprague-Dawley rats was presented in the HED. An increase in the thyroid follicular cell adenoma was noted, but was not statistically significant.

Table 3. Tumor incidences in rats fed diets containing Ethyl Parathion.

Male Wistar rats; 2-year study (Eiben, 1987)

Tumor Site/Type	0 ppm	2 ppm	8 ppm	32 ppm
Pancr. basophilic foci,	0/50 (0%)	0/50 (0%)	3/49 (6%)	2/50 (4%)
Pancr. acinar hyperplasia	0/50* (0%)	0/50 (0%)	1/49 (2%)	3/50 (6%)
Pancr. exocrine adenoma	0/50 (0%)	0/50 (0%)	1/49 (2%)	3/50 (6%)
Pancr. exocrine adenoma/carcinoma	0/50* (0%)	0/50 (0%)	1/49 (2%)	4/50 (8%)
Pancr. islet cell adenoma	0/50* (0%)	0/50 (0%)	1/49 (2%)	3/50 (6%)

Male Osborne-Mendel Rats; (dose: 80-wk TWA) (NCI, 1979)

Tumor Site/Type	Pooled Contr	0 ppm	32 ppm	63 ppm
Pancr. Islet cell carcinoma	0/79* (0%)	0/9 (0%)	1/49 (2%)	3/46* (7%)
Adrenal cort. adenoma	2/80** (4%)	0/9* (0%)	5/49 (10%)	9/46** (20%)
Adrenal cort. adenoma/carcinoma	3/80** (4%)	0/9* (0%)	7/49* (14%)	11/46** (24%)
Thyroid foll. adenoma	5/76* (7%)	3/10 (30%)	2/46 (4%)	8/43* (19%)

Female Osborne-Mendel Rats; (dose: 80-wk TWA) (NCI, 1979)

Tumor Site/Type	Pooled Contr	0 ppm	23 ppm	45 ppm
Adrenal cort. adenoma	4/78** (5%)	1/10* (10%)	4/47 (9%)	11/42** (26%)
Adrenal cort. adenoma/carcinoma	4/78** (5%)	1/10* (10%)	6/47 (13%)	13/42** (31%)

The \* ( $p < 0.05$ ) and \*\* ( $p < 0.01$ ) are levels of statistical significance for trend test (given at the controls) and Fisher's Exact test (given at the dose levels). The pair-wise comparison in the NCI study was against the pooled controls.

In conclusion, the studies in rats showed some evidence of oncogenicity: (1) two types of pancreatic tumors in two strains (Wistar and Osborne-Mendel) and (2) adrenal cortical tumors in both sexes of Osborne-Mendel rats.

#### Studies in Mice

Two studies in mice, the NCI study (1979) and a recently submitted study, were available for the evaluation of oncogenicity. As presented in the HED, no evidence of oncogenicity was shown in the NCI study (1979).

In a recently submitted study (Page and Heath, 1991) groups of 50 B6C3F1 mice per sex were fed diets containing 0, 60, 100, or 140 ppm ethyl parathion for 18 months. Mice at 60 ppm were mistakenly given diets at approximately 500 ppm from day 300 to day 307. Incidences of tumors with significant increases in the treatment groups were presented in Table 4. There was a positive trend for systemic malignant lymphoma in the males but the incidences were within the historical values. No treatment-related effects in the incidence of malignant lymphoma were indicated in the NCI (1979) study with the same dose range and at comparable dose levels. The significant increases in lung tumors at the low dose were difficult to interpret due to the misdosing. The evidence of oncogenicity in mice was judged as equivocal.

Table 4. Tumor incidences in B6C3F1 mice fed diets containing Ethyl Parathion (data from Page and Heath, 1991).

	0 ppm	60 ppm	100 ppm	140 ppm	His. Control
<u>Males</u>					
Malig. Lymphoma	0/50** (0%)	0/50 (0%)	2/50 (4%)	4/50 (8%)	15/150 (10%)
Lung A/B adenoma	5/50 (10%)	13/50* (26%)	6/50 (12%)	4/50 (8%)	16/150 (11%)
Lung A/B adenoma/ carcinoma	5/50 (10%)	14/50* (28%)	6/50 (12%)	4/50 (8%)	26/150 (17%)
<u>Females</u>					
Malig. Lymphoma	0/50 (0%)	5/50* (10%)	3/50 (6%)	2/50 (4%)	41/150 (27%)

The \* ( $p < 0.05$ ) and \*\* ( $p < 0.01$ ) are levels of statistical significance for trend test (given at the controls) and Fisher's Exact test (given at the dose levels).

The Peer Review Committee of Health Effects Division, U.S. EPA (1989), considered the evidence in the three rat studies, the NCI mouse study, and the mutagenicity, concluded that ethyl parathion should remain in Group C, Possible Human Carcinogen, of the carcinogen classification and recommended against taking a quantitative approach in risk assessment.

## V. RISK CHARACTERIZATION

The most appropriate approach to evaluate the oncogenic potential in humans is currently being determined. Although the oncogenicity is not used as a basis for the TAC listing recommendation, it will be considered in the next phase of AB1807 implementation - the decisions regarding control measures.

Non-oncogenic endpoints of toxicity are assessed in this section. The same air concentrations (see Section III. EXPOSURE ASSESSMENT) used in the HED for various exposure scenarios are also used in this assessment. In estimating the exposure, the respective respiratory rates for rats and human adults and children at 0.96, 0.26, and 0.46 m<sup>3</sup>/kg/day were assumed. These values were also used in the HED. Margins of safety (MOSSs) were calculated as the ratio of NOEL to exposure.

The MOS based on ChE inhibition has been presented in the HED (Appendix A). This document presents an additional set of MOS values based on endpoints of better defined adverse health effects.

For the acute exposure, the estimated NOEL of 0.16 mg/m<sup>3</sup> (4-hr) or 0.026 mg/m<sup>3</sup> (24-hr) was used. This value was based on lacrimation as a cholinergic sign of toxicity determined in the rat teratology study. The NOEL of 0.63 mg/m<sup>3</sup> (4-hour) or 0.1 mg/m<sup>3</sup> (24-hour) based on functional impairment of the eye detected in the rats was also used to assess the risk of acute exposure. For the subchronic exposure scenarios, the TWA dose of 0.02 mg/kg/day (equivalent to 0.08 mg/m<sup>3</sup> for adults and 0.04 mg/m<sup>3</sup> for children) determined in humans was used. The NOEL of 0.04 mg/kg/day based on abnormal ERG in rats was also used, as there was no indication that this endpoint was examined in the human study. For the chronic exposure scenarios, a NOEL of 0.4 mg/kg/day (ocular effects, body weight gain reduction, and tremors) established in a 2-year rat study was used. This NOEL was higher than that for acute exposures because the endpoints in acute studies were either not reported or not examined in the chronic studies.

The MOSSs are presented in Table 5. At the off-site 4-hour air concentration of 34 ug/m<sup>3</sup>, the acute MOSSs of 10 to 17 (based on signs of ChE inhibition in rats) and 38 to 68 (based on ocular effects in rats) were considered not adequate. At the ambient air concentration of 1.4 ug/m<sup>3</sup>, the MOS of 39 to 69 (based on signs of ChE inhibition in rats) was also considered not adequate for the protection of human health. The subchronic MOSSs are at least 260

Table 5. The Margins of Safety (MOSS) for Potential Exposures to Ethyl Parathion in Air.

Effects	NOEL	Human Equivalent		Exposure (ug/m³)	MOS	
		Adult	Child		Adult	Child
		(mg/m³)				
<u>ACUTE EXPOSURE - Off-Site</u>						
cholinergic signs (lacri- mation) in rats	0.16 (mg/m³) (4-hour)	0.58	0.33	34 3.1	17 190	10 110
ocular function in rats	0.63 (mg/m³) (4-hour)	2.31	1.30	34 3.1	68 740	38 420
<u>ACUTE EXPOSURE - Ambient</u>						
cholinergic signs (lacri- mation) in rats	0.026 (mg/m³) (24-hour)	0.1	0.05	1.4	69	39
ocular function in rats	0.1 (mg/m³) (24-hour)	0.38	0.22	1.4	270	160
<u>SUBCHRONIC EXPOSURE</u>						
lack of effects in humans	0.02 mg/kg/day	0.08	0.04	0.17	450	260
ocular function in rats	0.04 mg/kg/day	0.15	0.087	0.17	900	510
<u>CHRONIC EXPOSURE</u>						
ocular, tremors, body weight in rats	0.4 mg/kg/day	1.54	0.87	0.17	9,100	5,100

based on the NOEL in humans and 510 based on the NOEL in rats. They are considered adequate. The chronic MOSs are above 5,000 and do not indicate any health concern.

## VI. DISCUSSION

Areas of uncertainty exist in the risk assessment of ethyl parathion. One of the area is in the exposure assessment. Under the specific application condition, the 34 ug/m<sup>3</sup> is likely an overestimation whereas the 3.1 ug/m<sup>3</sup> an underestimation of a 4-hour parathion concentration. These values, however, did not account for the presence of paraoxon which was quantified in other studies (Woodrow et al., 1977). Paraoxon is approximately 10-fold more toxicologically potent than parathion (HED, P.91). Moreover, the use restrictions, both for now and after July 1992, may further impact the exposure estimation. Other areas of uncertainty were also introduced in the assumptions used in characterizing the risk. For example, in deriving an inhalation NOEL from an oral NOEL, it was assumed that the absorption was equal for the two routes of exposure and that the 4-hour NOEL was 6 times of the 24-hour NOEL. The available data do not allow a further refinement of the assessment.

A list of air concentrations that will provide adequate MOSs for non-oncogenic effects under the various exposure scenarios is presented in Table 6. This does not take into account the exposures through other routes, such as dietary and occupational exposures.

## VII. TAC LISTING RECOMMENDATION

This document presents the rationale for a TAC listing recommendation based on both the assessment provided in the HED and the assessment using the same air concentrations but alternate endpoints.

### TAC LISTING BASED ON THE HED

It was stated in the HED that an MOS of 10 for an adult or 20 for a child may be needed for the protection of health when the NOEL was based on ChE inhibition above 30%. Applying the extra 10-fold factor as specified in the Criteria for Identifying Pesticides as Toxic Air Contaminants, an MOS within 100 for an adult or 200 for a child, based on ChE inhibition and in the absence of signs of toxicity, will thereby trigger the recommendation for TAC listing.

The MOSs based on ChE inhibition was presented in the HED (See also Appendix A). Although the subchronic MOSs were as low as 12, they do not trigger a recommendation for listing because the MOSs based on human data exceeded 200. The latter required no interspecies extrapolation, was judged pertinent, and therefore, is preferred over the conclusion based on animal data. The acute MOS of 74 (child) and the chronic MOS of 100 (child) were below 200.

Table 6. Air Concentrations corresponding to Adequate MOSs for Non-oncogenic Effects.

Effects	NOEL	<u>Human Equivalent</u>		MOS	<u>Threshold Air Conc</u> (ug/m <sup>3</sup> )
		Adult	Child		
		(mg/m <sup>3</sup> )			
<u>ACUTE EXPOSURE</u>					
cholinergic signs (lacri- mation) in rats	0.026 (mg/m <sup>3</sup> ) (24-hour)	0.1	0.05	100 100	0.5 (child; 24-hr) 3.3 (child; 4-hr)
ocular function in rats	0.1 (mg/m <sup>3</sup> ) (24-hour)	0.38	0.22	100 100	2.2 (child; 24-hr) 12.5 (child; 4-hr)
<u>SUBCHRONIC EXPOSURE</u>					
lack of effects in humans	0.02 mg/kg/day	0.08	0.04	10	4.0 <sup>a</sup> (child)
ocular function in rats	0.04 mg/kg/day	0.15	0.087	100	0.9 (child)
<u>CHRONIC EXPOSURE</u>					
ocular, tremors, body weight in rats	0.4 mg/kg/day	1.54	0.87	100	8.7 <sup>b</sup> (child)

<sup>a</sup>Eye function, which was not examined in the human study, appeared to be a more sensitive endpoint. Visual deficit in rats was indicated.

<sup>b</sup>The endpoints in acute studies were either not reported or examined in the chronic studies. As a result, the chronic threshold is higher than the acute threshold.

Therefore, it is recommended that ethyl parathion be listed as a TAC.

#### TAC LISTING BASED ON ADDITIONAL TOXICOLOGY DATA

The MOSSs based on endpoints other than ChE were presented in Table 5. In general, an MOS of 100, based on endpoints with defined biological significance, is required for the protection of health. Applying the extra 10-fold factor as specified in the Criteria for Identifying Pesticides as Toxic Air Contaminants (Section 6890, Title 3, California Code of Regulation), an MOS below 1,000 will trigger the listing. Based on both the acute and the subchronic MOSSs (below 1,000), ethyl parathion is recommended for listing as a TAC.

In conclusion, ethyl parathion is recommended for listing as a TAC. This conclusion is based on both the assessment initially presented in the health effects document and also the assessment presented in this document using endpoints other than cholinesterase inhibition which included cholinergic signs and ocular effects.

## REFERENCES

- Ahmed, F. E. 1981 One year feeding study in the dog. Pharmacopathics Research Labs, Inc., Report #7832. DPR Vol. 50468-001, #14995.
- Atkinson, J. E. 1991a An acute oral toxicity study in the rat with ethyl parathion. Bio/dynamics Inc., Project No. 89-3458. DPR Vol. 50468-061, #96699.
- Atkinson, J. E. 1991b A three month oral toxicity study in rats via the diet with ethyl parathion to investigate ocular effects and cholinesterase activity. Bio/dynamics Inc., Project No. 89-3469. DPR Vol. 50468-062, #96700.
- Atkinson, J. E. 1991c A six month oral study of ethyl parathion in dogs with specific emphasis on ocular effects. Bio/dynamics Inc., Project No. 89-3439. DPR Vol. 50468-063, #96686.
- Cuthbert, J. A. and S. M. A. Carr. 1986 Ethyl parathion 98% technical: Acute toxicity tests. Inveresk Research International Report # 234117, DPR Vol. 50468-34, #72067.
- Eiben, R. 1986 Parathion: Chronic toxicology study in rats. Bayer AG Report #T1016770. DPR Vol. 50468-028, #50707
- Eiben, R. 1987 Parathion: Study for chronic toxicity and cancerogenicity in Wistar rats. DPR Vol. 50468-035, #72066.
- Eiben, R. 1989 Historical incidence of tumors taken from studies with Wistar rats. DPR 50468-051, #85343.
- Department of Pesticide Regulation, Cal-EPA. 1990 Summary of Toxicology Data for Ethyl Parathion.
- Greenough, R. J. and P. McDonald. 1986 Ethyl parathion 98% technical acute inhalation toxicity study in rats. Inveresk Research International, Report # 3476. DPR Vol. 50468-034, #72068.
- Maddy, K. T., D. Gibbons, D. M. Richmond, and A. S. Fredrickson. 1983 A study of downwind drift of parathion from applications in the antelope valley of Los Angeles county, California in April 1982. DPR Report HS-1087
- Morgan, D. P., H. L. Hetzler, E. F. Slach, and L. I. Lin. 1977 Urinary excretion of paranitrophenol and alkyl phosphates following ingestion of methyl or ethyl parathion by human subjects. Arch. Environ. Contam. Toxicol. 6:159-173.
- National cancer Institute (NCI), 1979. Bioassay of parathion for possible carcinogenicity. NCI-CG-TR-70.

Oudiz, D. and A. K. Klein. 1988 Evaluation of ethyl parathion as a toxic air contaminant. DPR Report #EH-88-5.

Owens, E. J. 1977 The effects of ethyl parathion in the rat and dog after acute and subacute inhalation and oral administration. Aerosp. Med. Res. Labs., Proc. Annu. Conf. Environ. Toxicol. 7th; p.203-222.

Page, J. G. and J. E. Heath. 1991 Carcinogenicity study of ethyl parathion administered by dosed feed to B6C3F1 mice. Southern Research Institute, Project A21-CRM-1. DPR Vol. 50468-060, #089300.

Rider, R. T., H. C. Moeller, J. I. Swader, and R. W. Weilestein. 1958 The effect of parathion on human red blood cell and plasma cholinesterase. Section II. Arch. Ind. Health 18:442-445.

Schroeder, R. E. 1983a A teratogenicity study in rats. Bio/dynamics Project 82-2644. DPR Vol. 50468-005, #11161.

Schroeder, R. E. 1983b A teratogenicity study in rabbits. Bio/dynamics Project 82-2660. DPR Vol. 50468-005, #11163.

U. S. EPA (1989) Second peer review of parathion. U. S. EPA, Washington, D.C., Office of Pesticide and Toxic Substances, Health effects Division.

U.S. EPA (1991) Ethyl parathion, receipt of requests for cancellation, maintenance fee cancellation, cancellation order, notification requirement, memorandum of agreement, request for comment on tolerance reduction/revocation. Federal Register 56:65061-65073.

Woodrow, J. E., J. N. Seiber, D. G. Crosby, K. W. Moilanen, C. J. Soderquist, and C. Mourer. 1977 Airborne and surface residues of parathion and its conversion products in a treated plum orchard environment. Arch. Environ. Contam. Toxicol. 6:175-191.

Appendix A  
Table 18 of Health Effects Document - Summary of Risk

TABLE 18  
SUMMARY OF RISKS

Effect <sup>a</sup>	Dose	Human Equivalent		Exposure <sup>d</sup>	Margin of Safety	
		Adult	Child		Adult	Child
<u>Acute:</u>						
NOEL, AChEI rat	1.21 mg/m <sup>3</sup> (4 hr)	4.48 <sup>b</sup>	2.50 <sup>b</sup>	34 ug/m <sup>3</sup> 3.09 ug/m <sup>3</sup>	100 1500	74 800
NOEL, AChEI rat	1.21 mg/m <sup>3</sup> (4 hr)	0.75 <sup>c</sup>	0.42 <sup>c</sup>	1.423 ug/m <sup>3</sup>	500	300
<u>Subchronic:</u>						
NOEL, AChEI rat	0.01 mg/m <sup>3</sup> (7 hr)	0.011 <sup>c</sup>	0.006 <sup>c</sup>	0.170 ug/m <sup>3</sup>	65	35
NOEL, AChEI dog	0.01 mg/m <sup>3</sup> (7 hr)	0.004 <sup>c</sup>	0.002 <sup>c</sup>	0.170 ug/m <sup>3</sup>	24	12
NOEL, AChEI human, oral	0.05 mg/kg per day	0.19 <sup>c</sup>	0.11 <sup>c</sup>	0.170 ug/m <sup>3</sup>	1000	600
<u>Chronic:</u>						
NOEL, AChEI, ophthalmic effects-rat	2 ppm(diet) (0.10 mg/m <sup>3</sup> )	0.37 <sup>c</sup>	0.21 <sup>c</sup>	0.170 ug/m <sup>3</sup>	2200	1200
NOEL, AChEI dog	0.01 mg/kg/d (0.026 mg/m <sup>3</sup> )	0.039 <sup>c</sup>	0.02 <sup>c</sup>	0.170 ug/m <sup>3</sup>	200	100

- a. NOEL = no observed effect level; AChEI = acetylcholinesterase inhibition.  
b. mg/m<sup>3</sup>/4 hours  
c. mg/m<sup>3</sup>/day  
d. Exposure data from Tables 5c, 6 and 7.

Appendix B  
Summary of Toxicology Data

CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE  
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

ETHYL PARATHION

SB 950-042, Tolerance #50468  
Chemical Code 459

November 4, 1986  
Updated 2/26/87, 6/05/90 and 5/1/91

I. DATA GAP STATUS

Chronic rat:	No data gap, possible adverse effect
Chronic dog:	Data gap, inadequate studies, no adverse effect indicated
Oncogenicity, rat:	No data gap, possible adverse effect
Oncogenicity, mouse:	No data gap, possible adverse effect
Reproduction, rat:	No data gap, no adverse effect
Teratogenicity, rat:	No data gap, no adverse effect
Teratogenicity, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, possible adverse effect indicated
Chromosome effects:	No data gap, no adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	No data gap, no adverse effect <sup>a</sup>

-----  
Note, Toxicology one-liners are attached

In one-liner document and record number identifications below,

  \*\* indicates acceptable study

**Bold face** indicates possible adverse effect

Revision of 6/5/90 by Aldous and Gee, 5/1/91 by Gee  
Filename: T910501

All relevant records on file as of 5/1/91 were considered for this Summary. These include record numbers through 096700 (Document 50468-063), and one or more record numbers greater than 900000. C. Aldous, 6/5/90, Gee, 5/1/91.

<sup>a</sup> Although considered negative for delayed neuropathies in hens, there is evidence of neuromuscular effects in rodents.

*Handwritten:* 12/1/91

## II. TOXICOLOGY ONE-LINERS AND DISCUSSION

## COMBINED (CHRONIC/ONCOGENICITY)

## RAT

**\*\* 50468-035 072066** Eiben, R., "Parathion study for chronic toxicity and cancerogenicity in Wistar rats (Administration in diet for twenty-six months)". Bayer AG, Toxicology Division, Wuppertal, final report completed Dec. 15, 1987 (sign-off by Director of the Institute für Toxikologie, Dr. E. Löser). Translation completed Jan. 7, 1988. Fifty rats/sex/treatment were placed on 2-year study: dosage groups of 0, 2, 8, and 32 ppm. There was no NOEL for cholinesterase (ChE) inhibition, since modest but statistically significant and dose-related plasma and RBC ChE inhibition was observed at the low dose of 2 ppm at some time periods. This dose could be considered a NOAEL for ChE inhibition, since substantial inhibition (i.e. > 20%) was limited to higher dosages, and since ChE-inhibition-related clinical signs were limited to 32 ppm females (particularly tremors). The NOEL for effects other than ChE inhibition was 8 ppm, based on reduced body weights in both sexes (ca. 20 g in females, 30 to 40 g in males); also on slightly increased mortality in 32 ppm females. In addition, there were two possible adverse effects: pancreatic exocrine tumors in males (with total incidence of 0, 0, 1, and 4 in controls through increasing dosage groups), and eye lesions (most definitively seen as increased degree of retinal atrophy in 32 ppm males and females). Acceptable as a "combined" study. Aldous, 5/24/90.

50468-051 085343 Eiben, R., "Historical incidence of tumors taken from studies with Wistar rats". (EPA MRID #40644704). March, 1986. This compilation is intended to supplement the 1986 Bayer rat parathion study, above. Data were presented on many tumor types. Data corresponding to the 22 studies on pancreatic tumors reported on p. 103 of the 1986 parathion rat study (Bayer AG) were presented in this report (identical numbers of affected rats were presented, with nearly always the same numbers of rats "at risk" as were provided in the parathion study. An explanatory letter (dated 5/18/90, located at the front of Document 50468-051) identifies all of these historical data to represent the timeframe 1980 to 1988. All were Bayer studies, all used the same source of animals as the parathion study (Winkelmann, Borchon), and all rats were Bor Wistar strain, as in the parathion study, above. Aldous, 5/23/90 (no CDFA worksheet).

50468-051 085344 Bombard, E. et al., "Spontaneous tumors of 2000 Wistar TNO/W.70 rats in two-year carcinogenicity studies". Published historical control data from JEPTO 7:35-52 (1986). All studies apparently were performed at Bayer AG, Institute of Toxicology, Wuppertal, F.R.G., or at nearby contract laboratories. All rats were bred at Winkelmann, Borchon (same source as 1986 Bayer AG Parathion study). All studies were started between 1973 and 1976. Six of the 11 studies were evaluated by the same pathologist. Variability was greater between studies evaluated by the same pathologist than between different pathologists. There were 9 islet cell tumors out of a total of 523 male rats examined (1.7%); none were found in females. One of these studies had incidence of 2/34 (6%), comparable to incidence in the cited Parathion study. Interestingly, no exocrine pancreatic tumors were noted in either sex in these 11 studies. Note that these data are of a somewhat earlier time period than the cited parathion study, and that these data are not part of the historical data submitted with the cited study. Aldous, 5/8/90.

CH 5/11/91

50468-036 072061 Minor pagination corrections for 035:072066, above.

50468-028 050707 Preliminary report of study 035:072066, examined by C. Aldous, 2/26/87.

50468-004 11158 (Bio/dynamics, 1/23/84). Incomplete version reviewed by J. Schreider, 3/12/85. Ethyl parathion (95.1%) fed in the diet at 0, 0.5, 5.0 or 50 ppm with estimated intakes at 0, 0.02, 0.20 and 1.91 mg/Kg/day in males and 0, 0.03, 0.27 and 3.31 mg/Kg/day in females for 26-28 months; 60/sex/group; ChE NOEL= 0.5 ppm, other effects NOEL = 5 ppm (retinopathy at intermediate and high doses; neuropathy at high dose only, thyroid adenomas in high dose males); UNACCEPTABLE (early deaths in mid-dose males and high-dose females not explained; time-adjusted statistical analysis of pathology data is needed; more pathology narrative needed; discussion of hematology in high dose females needed; analytical methods for cholinesterase needed), possibly UPGRADEABLE with submission of the items requested by reviewer. J. Christopher, 10/16/85.

EPA ONE-LINER: oncogenicity follicular adenomas of thyroid 50 ppm, historical data required; tremors females 50 ppm, NOEL 5 ppm; abnormal gait females 50 ppm, NOEL 5 ppm; retinal degeneration females 50 ppm, NOEL, 5 ppm; depression all RBC values females 50 ppm, NOEL 5 ppm; depression plasma cholinesterase both sexes 5 ppm, NOEL 0.5 ppm; depression brain cholinesterase, both sexes, 50 ppm, NOEL 5 ppm; degeneration sciatic nerve 50 ppm, NOEL could not be determined. CORE GRADE: supplementary.

50468-008, 009, 010, 011, 012, 013, 014 34339, 34338, 34337, 34336, 34335, 34334 and 34333 Addenda to 11158.

50468-027 48663 Addendum to record #11158. Histopathology of peripheral nerve in middle and low-dose groups; data do not alter original one-liner or change the conclusions of that review (G. Patterson, 10/30/86).

50468-027 48664 Addendum to record #11158. These additional data on thyroid adenomas do not necessitate a revision in the one-liner or a change of the conclusions in the review (G. Patterson, 10/30/86).

#### CHRONIC

#### RAT

(See combined, rat, above)

#### DOG

50468-001 14995 "Ethyl Parathion: One Year Feeding Study in the Dog." (Pharmacopathics Research Laboratories, 8-20-81). Ethyl parathion (lot AK 1103, 95.5%) fed in the diet at 0, 0.01, 0.03 and 0.1 mg/Kg/day for one year; 8/sex/group; hematology, clinical chemistry and urinalysis prior to initiation and periodically until termination; no ophthalmology; no mortality; no adverse effects reported; there was a dose-related inhibition of cholinesterase activity, especially at 0.1 mg/kg with no clinical signs; UNACCEPTABLE (MTD not achieved, no justification of doses selected, tables of data cited in text are not included - last page is 145, Table #T-4.8.2 - incomplete report), NOT UPGRADEABLE. Schreider, 3/12/85, updated 4/3/91, Gee.

4511

EPA ONE-LINER: ChE NOEL < 0.01 mg/kg (LDT) (RBC, plasma and brain ChE were inhibited); CORE GRADE: minimum.

#### Supplemental subchronic studies

001 016095 "Fourteen Day Feeding Study in the Dog." (Pharmacopathics Research Laboratories, 9/12/77) Ethyl parathion, 99.7%, was fed in the diet at 0 (diet), 1.5, 3.0 or 6.0 mg/kg/day to 2/sex/group, beagle dogs. Emesis was the major clinical sign reported in a dose-related incidence. All dogs survived. Gross necropsy only with no observations reported. SUPPLEMENTAL to 014995. No worksheet. Gee, 4/3/91.

001 016094 "Ethyl Parathion: Ninety Day Feeding Study in Dogs." (Pharmacopathics Research Laboratories, 3/6/78) Ethyl parathion, 99.4%, was fed in the diet for 90 days to beagle dogs, 4/sex/group, at 0 (diet), 0.3, 1.0 or 3.0 mg/kg b. wt. per day. No mortality. SGOT and SGPT were slightly elevated in the high dose males at 6 and 13 weeks but not in females. Plasma and RBC cholinesterase levels were decreased in a dose-related manner in males and females with plasma showing a greater effect in both sexes. No inhibition of brain cholinesterase at 13 weeks. No compound-related necropsy or histological findings reported. ChE NOEL < 0.3 mg/kg b. wt./day. Systemic NOEL > 3.0 mg/kg/day. No diet analyses. SUPPLEMENTAL to 014995. No worksheet. Gee, 4/3/91.

063 096686 "A Six Month Oral Study of Ethyl Parathion in Dogs with Specific Emphasis on Ocular Effects." (J. E. Atkinson, Bio/dynamics, Inc., Project No. 89-3439, 3/21/91) Ethyl parathion, 98%, was given in gelatin capsules to 5 beagle dogs/sex/dose at 0 (corn oil), 0.0024, 0.0079 or 0.79 mg/kg/day for six months. Only gross lesions and the eyes were subjected to detailed examination. Cholinesterase activity was measured for plasma, RBC, pons and cerebellum of the brain, retina and ocular muscle. Electoretinograms were performed for functional impairment of the eye. No consistent findings other than cholinesterase inhibition at the high dose in both sexes were reported. The study is supplemental based on the design. Gee, 4/30/91.

#### ONCOGENICITY

##### RAT

(See also combined, rat, above)

50468-026 042902 (Gulf South Research, 1979, for NCI) Ethyl parathion, 99.5%, fed in the diet at 0, 32 or 63 ppm (TWA) to males and 0, 23 or 45 (TWA) to female Osborne-Mendel rats, 10/sex in concurrent controls and 50/sex/test group, for 80 weeks followed by 32-33 weeks of observation; onco NOEL < 32 ppm (TWA) in males and = 23 ppm (TWA) in females for increase in adrenal adenomas/carcinomas; UNACCEPTABLE (no individual data, no periodic analysis of diet is presented, no hematology, clinical chemistry or urinalysis was performed, inadequate number of concurrent controls.) Incidence of adrenal cortical adenomas/carcinomas in males was 0/9, 7/49 and 11/46 in control, low and high dose groups with 3/80 in pooled controls. In females, the incidence was 1/10, 6/47 and 13/42 with 4/78 in pooled controls. The incidence of pancreatic islet-cell carcinomas in males was 0/9, 1/49 and 3/46 with 0/79 in pooled controls. Body tremors in the second six months occurred in 25/50 of the high dose females. J. Gee, 11/3/86.

## Page 5

EPA 1-liner: No grade. Oncogenic NOEL = 32 ppm (male), 23 ppm (female) (increased adrenal cortical adenomas); systemic NOEL < 32 ppm (male), < 23 ppm (female) (decreased body weight, tremors, hyperexcitability).

## ONCOGENICITY

## MOUSE

50468-026 927590 (Gulf South Research, 1979, for NCI) Ethyl parathion, 99.5%, fed to B6C3F1 mice, 10/sex for concurrent control, 50/sex/treatment group, fed at 0, 80 or 160 ppm; males for 71 (low) or 62 (high) weeks, females for 80 weeks. No adverse chronic or oncogenic effects; some behavioral signs and decreased body weight gain in males (data in graph form only); onco NOEL > 160 ppm, systemic NOEL cannot be determined from data as presented; UNACCEPTABLE (no individual data, no hematology, clinical chemistry, urinalysis, no analysis of diet to verify doses, two doses only, inadequate number of concurrent controls, housing of animals from several studies in one room.) J. Gee, 11/3/86.

EPA 1-liner: No grade. Oncogenic NOEL > 160 ppm (HDT), systemic NOEL, 80 ppm (LDT) (depressed body weights, tremors, hyperactivity, and hyperexcitability.) NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 2/6/89) notes EPA classification as "Core Supplementary".

**\*\* 060 (17 parts) 089300 "Carcinogenicity Study of Ethyl Parathion Administered by Dosed Feed to B6C3F1 Mice."** (Page, J. G. and Heath, J. E., Southern Research Institute, Birmingham, Alabama, project A21-CRM-1, 2/21/91) Ethyl parathion, lot/batch #DK-7620/70818-01, 96.7%, was fed in the diet to B6C3F1 mice at 0, 60, 100 or 140 ppm for 18 months. There were 50/sex/group with satellite groups of 35/sex for control and 140 ppm doses. Due to technical error, 60 ppm groups received approximately 500 ppm days 300 to 307 of the study, resulting in a few deaths. Cholinesterase inhibition was measured at 10 days, 12 and 18 months in control and 140 ppm sentinel animals. Plasma, RBC and brain inhibition was significant at 140 ppm. Signs of cholinesterase inhibition (labored breathing, hypoactivity, tremors) were noted, especially early in the study. Body weights were lower at 100 and 140 ppm, with males more affected than females. A possible adverse effect is noted for systemic malignant lymphoma in males with incidences of 0/50, 0/50, 2/50 and 4/50 with increasing doses and a positive trend test of  $p = 0.008$  - these incidences are within historical control values. The incidence of lung alveolar/bronchiolar adenomas in males is difficult to interpret because of the misdosing: 5/50, 13/50, 6/50 and 4/50 with increasing doses - no positive trend test. Study is acceptable. (Gee, 4/1/91)

## REPRODUCTION

## RAT

**\*\* 50468-006 011160 "A Two-generation Reproduction Study."** (Biodynamics, Project 80-2457, 8/18/82). Ethyl parathion (95.1%) was fed in the diet at 0, 0.5, 5.0 and 25 ppm to CD rats for 14 weeks before mating the F0 parents and approximately for 18 weeks before mating the F1 parents; 2 generations; 15 males per group, 30 females per group; histopathology on 10/sex/group F1 adults and 5/sex/group F1 and F2 weanlings; gross postmortem exam for all F0 and F1 parents, all weanlings; diets analyzed for content and homogeneity; no adverse effects reported; parental NOEL = 5 ppm (decreased body weight gain,

anogenital staining in 4/30 high dose females); ACCEPTABLE. Schreider, 3/15/85, updated 4/3/91, Gee.  
No EPA 1-liner.

## TERATOGENICITY

## RAT

\*\* 50468/005 011161 "A Teratogenicity Study in Rats." (Biodynamics, project BD-82-081, 8/26/83). Ethyl parathion (95.1%, lot AK-1144) was tested at 0 (corn oil), 0.25, 1.0 and 1.5 mg/Kg/day by gavage on days 6-19 of gestation with 24 CD rats per group; doses were 85 - 106% of nominal; no adverse developmental effects reported; maternal NOEL = 1 mg/kg/day (decreased weight gain, mortality of 4/24 high dose dams - cause not stated); lacrimation - a cholinergic sign - was seen at increased incidence in all treatment groups at day 6 (2, 15, 14 and 17 for controls and increasing doses), at day 10 (6, 9, 16 and 18) and day 15 (3, 6, 20 and 14) - considered an acute reaction; developmental NOEL > 1.5 mg/kg/day. ACCEPTABLE. Schreider, 3/14/85, updated by Gee, 4/3/91.

EPA ONE-LINER: Teratogenic NOEL > 1.5 mg/kg (HDT); fetotoxic NOEL > 1.5 mg/kg; maternal NOEL = 1 mg/kg (mortality, decreased weight gain, chromodacryorrhea); CORE GRADE: guideline.

50468-005 011162 Range finding study for 011161. Doses used were 0, 0.25, 0.5, 1.0, 2.0 and 4.0 mg/kg/day. Schreider, 3/13/85.

50468-016 036105 "Study for Embryotoxic Effects on Rats after Oral Administration." (Bayer, 9/4/84). Ethyl parathion (98.8%) tested at 0, 0.1, 0.3 and 1.0 mg/Kg/day by gavage on days 6-15 of gestation; NOEL: Maternal toxicity = 0.3 mg/Kg, fetotoxicity = 0.3 mg/Kg; UNACCEPTABLE (no analysis of dosing solution, no presentation of test article assay, no individual necropsy data on dying animals, no individual clinical observations, insufficient explanation of the fetal examinations, insufficient explanation of experimental methods, no connection of malformations or skeletal variations with individual fetuses, no identification of dams with clinical observations), UPGRADEABLE. Schreider, 4/17/86.

## RABBIT

\*\* 50468-005 011163 "A Teratogenicity Study in Rabbits." (Biodynamics, Project BD-82-162, 11/4/83). Ethyl parathion (95.1%) was tested at 0 (corn oil), 1, 4, and 16 mg/Kg/day by gavage on days 7-19 of gestation, 18/group. No adverse effects were reported. Maternal NOEL = 1 mg/kg/day (weight loss and fur staining), developmental NOEL = 1 mg/kg/day (distended renal pelvis). ACCEPTABLE. Schreider, 3/13/85.

EPA ONE-LINER: Teratogenic NOEL > 16 mg/kg (HDT); fetotoxic NOEL = 1 mg/kg (with mortality and renal pelvis distention reported at 4 and 16 mg/kg; maternal toxic NOEL = 1 mg/kg (decreased weight gain); CORE GRADE: guideline.

005 11164 Range finding study for 11163.

50468-016 036106 "Study of Embryotoxic Effects on Rabbits after Oral Administration." (Bayer, 2/15/85). Ethyl parathion (98.8%) was tested at 0 (0.5% Cremophor), 0.03, 0.1, and 0.3 mg/Kg/day by gavage on days 6-18 of gestation with 15/group. No adverse effects reported including no skeletal

variations at any dose. UNACCEPTABLE (doses too low, no data on skeletal variations, no individual necropsy information, no individual fetal weights, no individual clinical observations). NOT UPGRADEABLE. Schreider, 4/17/86.

## MUTAGENICITY

## GENE MUTATION

NOTE: From the limited data available in study 50468-036:072085, parathion is considered positive for gene mutation in mammalian cells, even though an acceptable microbial *in vitro* study was negative. There was a single trial with CHO/HGPRT in which there was a clear increase in mutation frequency at a low concentration. If a new study were to be conducted in the same cell system, using a similar concentration range and successfully overcoming miscibility problems, the replacement study would be cause for the mutagenicity data base to be re-evaluated. As of now, the data requirement is filled by Record #072060, with a possible adverse genotoxic effect in Record #072085. Gee, 6/5/90.

\*\* 50468-036 072060 "Salmonella/Mammalian-Microsome Plate Incorporation Mutagenicity Assay (Ames Test) with a Confirmatory Assay." (Lawlor, T. E., Microbiological Associates, Rockville, MD; Study Number T5772.501014, 3/22/88) Ethyl parathion, technical grade, 97/98%, lot 70818-01, was tested with Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98 and TA100. Two trials with triplicate plates per concentration in each trial were run with and without activation with Aroclor 1254-induced male Sprague Dawley rat liver S9. Concentrations were 0 (DMSO), 667, 1000, 3333, 6667 or 10,000 ug/plate, nominal concentration. Slight to moderate precipitate was noted at 3333 ug/plate and higher. No evidence of an increase in reversion rates was reported. No adverse effect. Acceptable. Gee, 6/1/90.

50468-036 072085 "CHO/HGPRT Mutation Assay." (Yang, L. L., Microbiological Associates, Rockville, MD, Study Number T5772.332, 3/28/88) Ethyl parathion (97/98% technical) was tested for gene mutagenicity with Chinese hamster ovary cells in the presence and absence of activation with Aroclor 1254-induced male Fischer rat liver S9. Concentrations used were 0 (solvent and untreated), 0.03, 0.06, 0.1, 0.2 or 0.3  $\mu$ l/ml of medium, duplicate cultures in a single trial. Cells were incubated with ethyl parathion for five hours followed by 7 - 9 days of expression time. They were then plated for selection of mutants with 6-thioguanine. Parathion was not fully miscible at 0.06  $\mu$ l/ml and above. At 0.03  $\mu$ l/ml, the mutation frequency (mutants/ $10^6$  clonable cells) was increased significantly both with and without activation. Possible adverse effect of increase in mutation frequency. Unacceptable, not upgradeable (single trial). Gee, 6/1/90.

50468-016 036091 (Bayer, 6/25/80). Ethyl parathion (98.7-98.8%) tested at 0, 20, 100, 500, 2500, and 12,500 ug/plate +/- S9 on four strains of Salmonella - TA1535, TA1537, TA98 and TA100; 4 replicates; data suggest that there may be an effect but cannot evaluate; UNACCEPTABLE (incomplete and mislabeled tables, mean values only, no repeat trial), NOT UPGRADEABLE. Gee, 4/21/86.

## CHROMOSOMAL EFFECTS

\*\* 50468-036 072087 "Micronucleus Cytogenetic Assay in Mice: Final Report." (Putman, D. L., Microbiological Associates, Bethesda, MD, Study No. T5772.122, 3/24/88) Ethyl parathion (97/98% technical), lot 70818-01, was given by intraperitoneal injection to male and female CD-1 mice in a single dose. Doses were 0 (corn oil), 3, 13 or 26 mg/kg, 10 ml/kg. At 26 mg/kg, 31/40 were dead by 24 hours so the survivors were sacrificed for a 24-hour time-point. At the other doses, 5/sex were sacrificed at 24, 48 and 72 hours. One thousand polychromatic erythrocytes were scored per animal and the proportion of PCE's per total erythrocytes determined. It was necessary to run two attempts due to excess toxicity in the first trial (doses of 3, 17 or 34 mg/kg) and a problem with dosing solution preparation. No adverse effect. Acceptable. Gee, 6/4/90.

50468-036 072088 "Dominant Lethal Test on the Male mouse to Evaluate for Mutagenic Effect." (Herbold, B., Bayer AG, Institute of Toxicology, FRG, Report No. 14224, 1/15/86) Ethyl parathion (batch 230 300 004 - 008), 98.8%, was assayed for dominant lethal effects in male Bor: NMRI (SPF Han) mice. Fifty per group were given the vehicle (Lutrol) or 10 mg/kg ethyl parathion in a single oral dose. Males were mated 1:1 with untreated females, for 12 4-day mating periods. The dose selection was based on a preliminary test at 5, 10 or 20 mg/kg - all in the 20 mg/kg group died. Females were scored for corpora lutea, implantations, pre-implantation loss and living/dead implants. No adverse effect reported. Unacceptable, possibly upgradeable (no concurrent positive control group or acceptable substitute.) Gee, 6/4/90.

50468-016 036092 (Bayer, 3/29/82). Ethyl parathion (95.9%); 5/sex/group given 2 x 5, 2 x 10 or 2 x 20 mg/kg by oral gavage and sacrificed 6 hrs after second dosing; insufficient information to evaluate for possible effect; 3/10 deaths in mid dose and high dose was lost due to mortality; UNACCEPTABLE (protocol does not conform to guidelines, problems with dose selection) NOT UPGRADEABLE. Gee, 4/21/86.

## DNA DAMAGE/REPAIR

\*\* 036 072086 "Unscheduled DNA Synthesis in Rat Primary Hepatocytes." (Curren, R. D., Microbiological Associates, Rockville, MD, Study No. T5772.380, 3/28/88) Parathion (97/98% technical), 95% purity, was tested with primary rat hepatocytes from a male Sprague-Dawley rat. Concentrations were selected from a preliminary trial measuring cytotoxicity by release of lactic acid dehydrogenase. Final concentrations used were 0 (DMSO and medium), 0.0001, 0.0003, 0.0006, 0.001, 0.003, 0.006, 0.01 and 0.03  $\mu$ l/ml. The three highest concentrations were too toxic to score. Triplicate coverslips were exposed per concentration with 50 nuclei per coverslip scored by net nuclear grain counts from  $^3$ H-thymidine incorporation. Dimethylbenz(a)anthracene was the positive control and induced significant unscheduled DNA synthesis. There was no evidence of UDS with parathion. No adverse effect. Acceptable. Gee, 6/4/90.

## NEUROTOXICITY

Final Report

No neurotoxicity study is required at this time. CDFA has reviewed the data on parathion effects on delayed peripheral neuropathies, (Oudiz, D. and Klein, A.K., "Evaluation of ethyl parathion as a toxic air contaminant", 1988, CDFA Report Number EH-88-5). These authors found that the potential of parathion to produce delayed peripheral neuropathies is very small. They cited hen studies involving single high doses or repeated moderate dosages, which did not lead to delayed peripheral neuropathies. They noted that one rat chronic study (Daley, I.W., 1984, Bio/dynamics Study No. 77-2055, CDFA Record 50468-004:011158) indicated some evidence of distal neuropathies at the high dose of 50 ppm. More recently, a rat chronic/oncogenicity study, which has been accepted by CDFA and EPA, was negative for neuropathies at the high dose of 32 ppm [see review of this study, (Eiben, R., "Parathion study for chronic toxicity and cancerogenicity in Wistar rats (Administration in diet for twenty-six months)", Bayer AG, Toxicology Division, Wuppertal, final report completed Dec. 15, 1987, CDFA record 50468-035:072066)]. The latter study found no indications of delayed neuropathies at the high dose of 32 ppm. Hens are considered better surrogates than rats to evaluate delayed peripheral neuropathies. Given the large body of negative data in hens, and recognizing the precautions which must be taken to prevent substantial parathion exposure because of its marked acute toxicity, CDFA has no need of a hen neurotoxicity study to support SB-950 requirements at this time. Aldous, 5/25/90.

50468-036 072089 Neal, B., "Review of literature on the potential for delayed neurotoxicity associated with exposure to ethyl parathion". Author concludes that the vast majority of studies indicate that parathion is unlikely to elicit delayed distal neuropathy in humans. Many significant publications are reprinted in this record. It has been common practice to use ethyl parathion as a negative control for delayed distal neuropathy studies, since acutely toxic doses have repeatedly proved negative for delayed neuropathies in sensitive species. A single case report of a human exposure which was linked with paralysis of peroneus muscles has been noted for CDFA Hazard Assessment Group to consider (1950 article by von Petry, cited on p. 20 of 1976 NIOSH Criteria Document: Criteria for Occupational Exposure to Parathion). With the exception of that case report, and considering the substantial body of information on human exposure (which has occurred by accident or by experimental design), there is very little reason at this point to request further studies on possible delayed distal neuropathy potential in humans. Aldous, (no written CDFA review), 5/25/90.

#### MISCELLANEOUS

Risk assessment in Bioassay of Parathion for Possible Carcinogenicity by NCI.

#### SUPPLEMENTARY STUDY

062 096700 "A Three Month Oral Toxicity Study in Rats via the Diet with Ethyl Parathion to Investigate Ocular Effects and Cholinesterase Activity." (J. Atkinson, Bio/dynamics, Inc., Project No. 89-3469, 2/28/91) Ethyl parathion, technical, 98%, was fed in the diet for 3 months to female CD (Sprague-Dawley derived) rats at 0 (diet), 0.04, 0.4 or 4.0 mg/kg. The study was designed to determine the relationship between cholinesterase inhibition with dose and time and functional impairment of the eye as measured by electroretinography. There were 10 per group with pretest, 6 week and 3 month samplings and exams. Both light and electron microscopy were performed on the eyes. Although other tissues were saved, no histology was done. Effect: The

results indicate that cholinesterase inhibition and functional impairment coincide and occur as low as 0.4 mg/kg. SUPPLEMENTAL STUDY. Gee, 4/25/91.

121  
121  
121